UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/910,483	07/19/2001	Fang Fang	014357/027 8772	3201

7590 03/10/2006

PERLAN THERAPEUTICS, INC
6310 NANCY RIDGE DRIVE
SUITE 102
SAN DIEGO, CA 92121

EXAMINER	
LE, EMILY M	
ART UNIT	**PAPER NUMBER**
1648	

DATE MAILED: 03/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/910,483	FANG ET AL.	
	Examiner	Art Unit	
	Emily Le	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 September 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5-10,13,15-57 and 60-96* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5-10,13,15-57 and 60-90* is/are rejected.

7)☒ Claim(s) *13,17-19,28-57,60-68,71-78 and 86-96* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *7/19/01, 12/03/01, + 11/10/03* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10//24/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 09/15/2005 has been entered.

Status of Claim(s)

2. Claims 2, 4, 11-12, 14 and 58-59 are cancelled. Claims 84-96 are added. Claims 1, 3, 5-10, 13, 15-57 and 60-96 are pending and under examination.

Drawings

3. The replacement sheets of drawings are objected for the following reason(s):

It is noted that the numerous errors are present in the drawings. The following are some of the noted errors,

A) It is unclear if Humiii or HumIII has the amino acid sequence set forth in SEQ ID NO: 39 and/or 45 as its heavy chain.

B) It is unclear if HumkI, HumKI or Hum kI has the amino acid sequence set forth in SEQ ID NO: 40 and/or 46 as its heavy chain.

C) It is unclear why there are multiple amino acid sequences listed for each heavy and light chains? For example, Figure 1 indicates that SEQ ID NO: 37, 38, 41 and 42 are the amino acid sequence of murine 1A6 antibody. Are all these sequences directed to different parts/components of murine 1A6 antibody? OR are these sequences representative of different derivatives of murine 1A6 antibody.

D) Again, the description provided in the specification for Figure 3 is not consistent with what is presented in Figure 3. For example, the description notes that the SEQ ID NO: 37 and 41 are the amino acid sequence of variable heavy chain of the murine 1A6 antibody. However, Figure 3 indicates that SEQ IDNO: 37 and 38 are amino acid sequence of murine 1A6 antibody.

Moreover, because of this lack of consistency, it is rather unclear what the amino acid sequence of murine 1A6. Is it SEQ ID NO: 37, 38 or both? Additionally, why more than one SEQ ID NO: is granted to the same amino acid sequence? This issue is consistently noted throughout the drawings and the specification.

In all instances, clarification and new corrected drawings are required. Furthermore, throughout the entire examination of this patent application, lots and lots of oversights has been noted in the drawings by the Office. The Office strongly suggests Applicant to clean up the drawings and its description accordingly.

Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

Specification

4. The disclosure is objected by the Office. The **disclosure is extremely confusion**. It is unclear what the amino acid sequence goes with which antibody. For example, previously, Applicant submits that SEQ ID NOs: 37 and 39 are the amino acid sequence of the Humiii heavy chain. However, as currently submitted, Applicant asserts that SEQ ID

NO: 39 and 45 are the amino acid sequence of the Humiii heavy chain. In the instant, it is unclear what happened to the original SEQ ID NO: 37. And it unclear how SEQ ID NO: 45 comes into play. A detailed clarification is requested, and appropriate correction is required.

Claim Objections

5. Claims 13, 17-19, 28-57, 60-68, 71-78 and 86-96 are objected to because of the following informalities:

6. Claims 91-96 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim. See MPEP § 608.01(n). Accordingly, the claims have not been further treated on the merits.

7. Claim 31 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 31, which depends on claim 30, which depends on claim 29, requires the nucleic acid sequence to be linked to an expression control element. However, claim 29 already requires the nucleic acid sequence to be linked to an expression control element. In the instant, because the nucleic acid of claim 29 is required to be linked to an expression control element, the requirement set forth in claim 31 only repeats the requirement set forth in claim 29. Thus, claim 31 fails to further limit claim 29. Appropriate correction is required.

8. Claims 28-33 are objected to because of the following informalities: Claim 32 is directed to a "cell" comprising a particular nucleic acid. In the instant, although the Office recognizes that it is not Applicant's intention to claim a product of nature, however, as presented the claims do read on a product of nature, a cell that contains the nucleic acid disclosed in claim 28. Thus, to provide additional clarity to the claims about Applicant's intention, the Office suggests the insertion of "An isolated" prior to the term "cell". The insertion would yield the recitation "An isolated cell" rather than the currently presented "cell". The implementation of the suggested changes would obviate this objection. The same analysis applies to claim 28, which recites a "nucleic acid sequence" without the implication that the claimed nucleic acid sequence is a non-naturally existing nucleic acid sequence.

This objection also carries over to claims that depend on claim(s) 28 and 32. Claims 29-33 are dependents of claim 28 and/or claim 32. Appropriate correction is required.

9. Claims 13, 17-19, 34-57, 60-68, 71-78 and 86-90 are objected to because of the following informalities: The claims are in improper multiple dependent form.

MPEP § 608.1 (n) sets forth: Any dependent claim which refers to more than one other claim ("multiple dependent claim ") shall refer to such other claims in the alternative only.

In the instant, the claims recite dependency to more than one claim. Appropriate correction is required.

Claim Rejections - 35 USC § 112

10. Claims 1, 3, 5-10, 13, 15-57 and 60-90 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 3, 13, 16-57, 60-78 and 85-90 contain the recitation "non-human donor amino acid". The cited recitation renders the claims indefinite. In the instant, the structural difference between an amino acid that is present in humans compared to an amino acid that is present in non-humans is unclear. The amino acid lysine is lysine irrespective of the species that the residue is present.

In response to the same rejection set forth in the previous office action, Applicant submits that the recitation is standard language used to reference interspecies amino acid positional substitutions and those in the art would find this language unambiguous when read in conjunction with the instant specification.

Applicant's submission has been considered but it is not found persuasive. MPEP § 2111.01 [R3] states the following: While the claims of issued patents are interpreted in light of the specification, prosecution history, prior art and other claims, this is not the mode of claim interpretation to be applied during examination. **During examination, the claims must be interpreted as broadly as their terms reasonably allow.** In re American Academy of Science Tech Center, **>367 F.3d 1359, 1369, 70 USPQ2d 1827, 1834 (Fed. Cir. 2004)< (The USPTO uses a different standard for construing claims than that used by district courts; **during examination the USPTO must give claims their broadest reasonable interpretation**.). This means that the words of the claim must be given their plain meaning unless applicant has provided a clear definition in the specification. In re Zletz, 893 F.2d 319, 321, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989) (discussed below);

Chef America, Inc. v. Lamb-Weston, Inc., 358 F.3d 1371, 1372, 69 USPQ2d 1857 (Fed. Cir. 2004)

In the instant, the Applicant has not provided a clear definition for the cited recitation in the specification. In the absence of a clear definition in the specification, the cited recitation is given its broadest meaning. And in defining the broadest interpretation for the cited recitation, the Office attempted to ascertain a reasonable metes and bounds for the cited recitation. However, the Office cannot ascertain the metes and bounds for the cited recitation. Thus, as presented, it is unclear what the metes and bounds are for the recitation "non human amino acids". As presented, the claims appear to be directed at amino acids that are not present in humans. And, it is unclear what kind or type of amino acids that are present in non-humans compared to humans. To overcome this rejection, Applicant can amend to claims to adopt the following language: wherein one region of the human framework is substituted with a region of a non-human, murine, framework.

Claims 79-83 are rendered indefinite because the claims recite a dependency to a cancelled claim, claim 4. Currently, the claims recite a dependency to claim 4, which is cancelled in Applicant's 09/15/2005 submission.

Claims 5-10, 13, 15-21 and 60-78 are rendered indefinite because it is unclear what is intended by the following recitation "wherein an acceptor variable framework region of SEQ ID NO: 5 and/or SEQ ID NO: 7 an amino acid substitution in a human consense variable region sequence".

Claims 5-10, 13, 15-21 and 60-78 recite the limitation "the protective efficacy" in claim 5, the independent claim. There is insufficient antecedent basis for this limitation in the claims.

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 36-57 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement for the full scope of the claimed invention. While specification is enabling for an *in vitro* method of inhibiting HRV infection, wherein the HRV uses the ICAM-1 receptor as the infective agent; however, the specification does not reasonably provide enablement for an *in vivo* method of inhibiting HRV. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In Genentech *Inc. v. Novo Nordisk* 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997); *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); See also *Amgen Inc. v. Chugai Pharm. Co.,* 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir. 1991); *In re Fisher* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Further, in *In re Wands* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) the court stated:

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman* [230 USPQ 546, 547 (Bd Pat App Int 1986)]. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.
>
> *Nature of the invention:*

The nature of the invention is directed at the inhibition of human rhinovirus (HRV) infection and the progression of human rhinovirus (HRV) infection and HRV associated symptoms--symptoms of the common cold with an antibody that blocks host cell receptor, the ICAM-1, used by HRV to gain entry into the cell.

Breadth of the claims:

The breadth of the claims includes decreasing and inhibiting any one or all of the symptoms of the common cold. The breadth of the claims also encompasses in vivo prevention of viral infectivity of HRV of all serotypes and treatment for HRV infections. And the population of interest includes humans and non-humans. The broadest claims are not limiting to a particular treatment population.

State of the prior art:

The art teaches that HRV serotype 1a does not use the ICAM-1 receptor to gain entry into the cells.[1] [Paragraph bridging pages 1506-1507 of Charles et al.] Thus, the blockage of the ICAM-1 receptor with an antibody does not prevent or inhibit the entry of HRV serotype 1a into a cell. Thus, the claimed invention is not enabling for HRV serotype 1a.

Additionally, the art cautions that in vitro efficacy do not necessarily translate in vivo. Specifically, the art teaches the murine version of the claimed antibody fails to prevent the on set of HRV induced diseases. Fang et al., Charles et al., and Le Calvez et al. notes

[1] Charles et al. Prevention of human rhinovirus infection by multivalent Fab molecules directed against ICAM-1. Antimicrobial Agents and Chemotherapy, 2003, Vol. 47, No. 5, 1503-1508.

that the murine 1A6 antibody of Colonno et al.[2] fails to prevent the onset of HRV induced disease and symptoms.[3, 4, 5]

In each instance, Fang et al., Charles et al. and Le Calvez et al. notes that the murine 1A6 antibody of Colonno et al. fail to have the necessary affinity to ICAM-1 to competively compete with HRV. In the instant, the art recognizes that a high level of functional affinity would be necessary to displace HRV binding to ICAM-1.

Presence or absence of working examples:

The specification contains working examples that are directed at the *in vitro* studies of antibody binding to ICAM-1 and the protective efficacy provided by the antibody against HRV infection. Hence, the specification is enabling for in vitro use of the antibody against HRV.

The specification does not contain any *in vivo* working examples. The specification does not contain any evidence suggesting or demonstrating that the claimed antibody would be effective in decreasing and inhibiting any one or all of the symptoms of the common cold, and the *in vivo* prevention of HRV viral infectivity and treatment for HRV infections.

Amount of direction or guidance presented:

Beside the *in vitro* experimentation(s) present in the specification, the specification does not contain any additional guidance or direction pertaining to the *in vivo* use of the

---

[2] Colonno et al. EP 459577.
[3] Fang et al. Viral receptor blockage by multivalent recombinant antibody fusion proteins: inhibiting human rhinovirus (HRV) infection with CFY196. Journal of Antimicrobial Chemotherapy, 2003, 1-3.
[4] Charles et al. Prevention of human rhinovirus infection by multivalent Fab molecules directed against ICAM-1. Antimicrobial Agents and Chemotherapy, 2003, Vol. 47, No. 5, 1503-1508.
[5] Le Calvez et al. Review: Biochemical prevention and treatment of viral infections-A new paradigm in medicine for infectious diseases. Virology Journal, 2004, Vol. 1, 12-17.

antibody to decrease and inhibit any one or all of the symptoms of the common cold, and the *in vivo* prevention of HRV viral infectivity and treatment for HRV infections. The specification does not teach how the in vitro protective level observed for the claimed antibody translates *in vivo*. The specification does not teach how the antibody's affinity to ICAM-1 translates to *in vivo*.

Additionally, the specification does not contain any analysis pertaining to the level of affinity the antibody must possess toward ICAM-1 to effectively inhibit the binding between ICAM-1 and HRV *in vivo*. All that is present in the specification is the presumption that the antibody would be capable of decreasing and inhibiting any one or all of the symptoms of the common cold, and the in vivo prevention of HRV viral infectivity and treatment for HRV infections.

Predictability or unpredictability of the art:

The art, as evidenced by Fang et al., Charles et al. and Le Calvez et al., teaches that *in vitro* success does not translate to *in vivo* success. The use of receptor blockage is not predictable.

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F. 2d 1557, 1562, 27 USPQ 2d 1510, 1513 (Fed. Cir. 1993).

Conclusion

13. No claims are allowed.

14. Additionally, the following allowable subject matter has been communicated to Applicant's representative:

A humanized antibody that binds to ICAM-1, wherein the antibody comprises SEQ ID NO: 5 and SEQ ID NO: 7.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Emily Le whose telephone number is (571) 272 0903. The examiner can normally be reached on Monday - Friday, 8 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (571) 272-0902. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jeffrey S. Parkin, Ph.D.
Primary Patent Examiner
Art Unit 1648

E.Le